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| 10/649,399 | 08/26/2003 | Ben-Zion Dolitzky | 1662/60903 | 6089 |

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| EXAMINER | |
|---|---|
| BERCH, MARK L. | |

| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/649,399 | DOLITZKY ET AL. | |
| | Examiner | Art Unit | |
| | /Mark L. Berch/ | 1624 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *14 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3,5-10,18,19,31,35,37-40 and 52-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *57,59-73 and 79-83* is/are allowed.

6)☒ Claim(s) *1-3,5-10,18,19,31,35,37-40,52-56,58 and 74-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *01/14/2008 (2)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 35 is rejected under 35 U.S.C. 102(b) as being anticipated by Harnden 1990, with Harnden 1989 supplemental.

In Harnden 1990, see the preparation in the first full paragraph on page 501. The crystallization is done from water. The claims recite among others, methanol/water. However, no limits are set on the ratio of the two solvents; the claim would read on e.g. one part per billion of methanol in water. Even the most tiny trace is enough to qualify (see ***SmithKline Beecham Corp. v. Apotex Corp.***, 74 USPQ2d 1398 (CAFC 2005)).

The sentence in which Harnden 1990 reports doing the hydrogenation of the 6-Cl intermediate to obtain the hydrate carries the footnote 8, which conveys that the reaction was done according to the procedure done in footnote 8. Footnote 8 is Harnden 1989. The hydrogenation of the 6-Cl intermediate does indeed appear in Harnden 1989 as 13 to 14. Therefore, we assume that the procedure used in Harnden 1990 was indeed the procedure used in Harnden 1989. This reaction is done in methanol itself; see paragraph bridging pages 1741-1742. The solvent was removed from the Famciclovir product. However, the solvent removal cannot be exhaustive since it is already known that this compound forms a solvate with methanol. In their example 7, the methanol was removed by heating for 65□

for 2 hours in a vacuum. This is probably much more drastic than what Harnden 1989 did, since "solvent removal" normally involves simple evaporation. The use of the rather drastic heating for 65□ for 2 hours in a vacuum indicates that ordinary solvent removal does not destory the methanol solvate, or does not destroy it completely. After the solvent is removed, one had at least some methanol solvate of Famciclovir.

Next, the material is taken up in water and extracted twice with chloroform. Applicants state, "Harnden 1989 discloses a process of preparing famciclovir requiring two steps of solvent removal. Thus, even if one were to assume for argument purposes only that the twice extraction with chloroform may carry several molecules of residual methanol, the residual methanol would have been removed." This misunderstands the process. The extraction with chloroform dissolves in the chloroform both the Famciclovir AND the methanol. As was established by the references cited previously, methanol and chloroform are miscible in all proportions.

Accordingly, when Harnden does the crystallization from water, there are traces of methanol present from the synthesis which were carried along from the chloroform extraction, and therefore the condition of claim 35 are met, insofar as the claims read on the methanol/water mixture.

Claims 1-3, 5-10, 18-19, 31, 37-40, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by with Harnden 1989; US 5017701, US 5066805; US 5138057, US 6846927, 6342603, Freerer, Geen, 6437125, and WO 200006573.

In Harnden 1989, note the crystallization of (14) from Ethyl acetate/hexane. In US 5017701, note column 7, line 31, where it is crystallized from hot n-butanol; the same is seen in example II-5 of 6342603. In US 5066805, see Column 3, where the solid appears to

be prepared by evaporation from a chloroform/methanol solution. In US 5138057, see Column 8, lines 11-12 and 33, where it was crystallized from Ethyl acetate/diethyl ether and from n-butanol. In 6846927, the product was recrystallized from n-butanol but then reslurried in n-heptane, stirred and filtered, i.e. triturated with n-heptane. In Freerer, the crystallization was done from hot isopropanol; see last example. A similar procedure was done with in example 9 of 6437125. In WO 200006573, see synthesis example 11, which has trituration with diethyl ether. In Brand, see page 5251, with crystallizing from aqueous acetone. In Geen, note 9c, crystallized from n-Butanol.

Insofar as Claim 31 is concerned, the references which recited n-butanol anticipate, and provide further evidence that this is Form II, since the same method is used. Insofar as Claim 18 is concerned, the reference which recites diethyl ether trituration anticipates, and provide further evidence that this is Form I, since the same method is used. Insofar as Claim 30 is concerned, the references which recite isopropanol anticipate, and provide further evidence that this is Form I, since the same method is used.

The traverse is unpersuasive. MPEP 2112 states:

"SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY

The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."

In this case, the "unknown property" is the particular crystalline form. This is unknown because the reference is silent on this property. MPEP 2112 goes on to state:

"A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection."

Again, the "CHARACTERISTIC" which the prior art is silent on is the crystalline form.

This is not an ordinary inherency situation where it is not explicitly stated what the product actually is. In every reference applied, the reference explicitly teaches exactly what the compound is. In fact, it is the opposite. In a normal inherency situation, the claim is of known structure, and the reference is of unknown structure. Here, the reverse is true, and hence the legal circumstances of inherency-in-the-prior-art do not apply. The only difference is the property about which the reference happens to be silent. Recitation of a property, inherently possessed by the prior art thing, does not distinguish a claim drawn to those things from the prior art, ***In re Swinehart***, 169 USPQ 226, 229.

See for example ***Ex parte Anderson***, 21 USPQ 2d 1241 at 1251, discussion of Rejection E. The claims had "numerical or functional values for certain properties which [the authors of the references] did not measure". The PTO presented no reasoning as to why the prior art material would have been expected to have those properties. Instead, the decision states, "There is ample precedent for shifting the burden to an applicant to

reproduce a prior art product whose final structure or properties are, at least, in part determined by the precise process used in its manufacture." (page 1253).

In another example, certain claims of ***Ex parte Raychem Corp.*** 25 USPQ2d 1265 required a linearity ratio of less than 1.2. The decision notes that neither reference discloses any values of the linearity ratio. The PTO presented no reasoning as to what the ratio would be expected to be in the references. The Decision states: "However, this does not end the inquiry since, where the Patent and Trademark Office is not equipped to perform the needed testing, it is reasonable to shift the burden of proof to Raychem to establish that (1) the argued difference exists...."

And indeed, there have been a number of cases in which applicants have pointed to silence of the prior art with regard to this or that property: ***In re Pearson***, 181 USPQ 641; ***In re Zierden*** 162 USPQ 102; ***In re Lemin***, 140 USPQ 273; ***Titanium Metals Corporation of America v. Banner***, 227 USPQ 773; ***In re Benner,*** 82 USPQ 49; In re Wilder, 166 USPQ 545; ***Ex parte Kucera***, 165 USPQ 332; ***General Electric Co. v. Jewel Incandescent Lamp Co.***, 67 USPQ 155; ***In re May***, 574 F.2d 1082, 1090, 197 USPQ 601, 607; ***In re Parker***, 43 USPQ 457. Such efforts to avoid anticipation on that basis invariably failed. Going further, if silence about properties of prior art compounds could be relied on, then one could not reject over references with no utility (see ***In re Schoenwald***, 22 USPQ2d 1671), since applicants could always insert the utility into the claim as a property.

It is well settled that the PTO can require an applicant to establish that a prior art product does not necessarily possess the characteristics of the claimed product when the prior art and claimed products are identical or substantially identical. An applicant's

burden under these circumstances was described in ***In re Best***, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977) as follows:

> Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, or 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products (footnote omitted).

Applicants previously argued, "specific crystalline forms ... are not properties of famciclovir as physical properties such as melting point or boiling point." This cannot possibly be agreed with. The physical form that a compound takes is of course a "property". A physical property is not the same thing as an e.g. biological property, but a physical form is still a property. Are applicants seriously arguing that X-ray diffraction peaks for example are not a property? At any rate the reference "Chemistry Research Guide - Physical & Chemical Properties" is cited, which says, "CRC Handbook of Chemistry and Physics. 84th ed. (Annual) Premier source for property data. Provides information (in tabular format) for organic and inorganic compounds and the elements. Property data includes molecular weight (mw), physical form ...." This demonstrates that, as the word is commonly used, property of a chemical compound includes physical form. The examiner just does not understand the basis for drawing the distinction here. For example, assuming that the compound is pure, the different melting points between two forms arises from there being two different crystalline forms (that is, different crystalline forms are expected to have different melting points). So it is not seen what basis there could possibly be for treating these two properties (crystalline habit, and melting point) differently.

Applicants now argue that these are "new products". This is the same Famciclovir. Unlike the usual inherency situation, where the identity of the material is unknown, the references teach exactly what the material is; it is Famciclovir. What is unknown is a property. When that situation arises, the above quotations from ***Best*** and ***Anderson*** and ***Raychem*** make it clear that the burden lies with applicants to show that the prior art material does not have this property.

If applicants' reasoning were accepted, then any anticipation rejection of an old compound could always be overcome by tacking on some characteristic or property which the reference was silent on, regardless of whether the prior art material was any different from the claimed material. For example, if it did not happen to mention the color, one could patent an old compound just by adding "which is green" or "which is not indigo". Applicants would then argue that their green material represents "new products", as opposed to the prior art material whose color was not mentioned. One could put in a limitation about density (e.g. "density is not 1.4"), melting point, "refractive index of 2.0", solubility in some uncommon solvent, spectroscopic data, and then simply point to the silence of the reference, as applicants have done here. Or one could add properties like or "does not explode on tapping" or "in the form of microneedles". Indeed, applicants could patent the same material over and over again, just tacking on a different characteristic each time.

The examiner notes for the record that the document "Third party observations" which applicants have submitted establishes that Example 2 of EP 182024 is in fact Form I. That example 2 is the same as Harnden 1989. The document also notes that 4(b) of EP 352953 gives Form II. That is the same as US 5017701.

Claims 53-56, 58 and 78 are rejected under 35 U.S.C. 102(b) as being anticipated by Harnden 1990, with Harnden 1989 supplemental.

Applicants have re-introduced claims to the methanol solvate.

Note the discussion of these references above. Harnden 1990 is considered to have inherently formed the methanol solvate. Judging from examples 7 and 8 in this specification, the methanol solvate forms spontaneously in methanol; no special crystallization method is needed to generate it. With regard to inherency, note the above discussion.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 35 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DMF/water, does not reasonably provide enablement for all other choices. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Brand teaches that the use of aqueous acetone gives famciclovir, not famciclovir hydrate. This then casts doubt on other aqueous solvents except for the aqueous DMF in the example.

The earlier traverses were unpersuasive. It is correct that Brand teaches that aqueous acetone gives famciclovir, but does not explicitly state that the product was Famciclovir and not famciclovir hydrate.

The examiner does not need rigorous proof. All that is needed is a reasonable basis to doubt. MPEP 2164.05 states, "Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary" that the claims are indeed enabled.

In response, applicants made two arguments. First, they state: "Especially because Brand used only $^{1}$H-NMR and $^{13}$C-NMR performed in solution, the NMR techniques used by Brand would not be expected to differentiate famciclovir from Famciclovir monohydrate."

This is simply untrue. First, Brand used elemental analysis to characterize the material, and all elements C, N and H were within proper error limits of the calculated for the non-hydrate. If this were actually the monohydrate, all three elements analysis would be outside the normal error ranges for the calculated percentage. Second, their reported melting point of 103-105□ is virtually identical, as noted by Brand, to the literature value of 102-103□. By contrast, Harnden 1990 reports 87-95□ for the monohydrate.

Applicants second argument is: "One skilled in the art would recognize that one may need to use $^{13}$C-solid-state NMR, preferably coupled with the use of high power proton decoupling, magic angle spinning and cross-polarization, to differentiate a crystalline substance from its hydrate." No evidence whatsoever is presented that such

techniques are needed. Harnden 1990 as well as EP 885223 both report the monohydrate without resort to such techniques.

Thus, the reference says that it is Famciclovir, and it has the correct elemental analysis for Famciclovir, and it has the melting point for Famciclovir, and not the melting point for Famciclovir monohydrate, and hence there is every reason to assume that the reference has exactly what it says it has.

Applicants now argue that " Brand also did not provide details on the procedure used to do the elemental analysis." What procedure is used to do the elemental analysis is rarely given because it does not matter. Elemental analysis of organic materials, except in the most unusual cases, is entirely conventional and needs no explanation. There is no reason to think that Brand erred in his elemental analysis.

Applicants also state: "Claim 35 recites the use of water mixed with ethanol, DMF, DMA, acetonitrile, methanol, THF or isopropanol, which was demonstrated by Example 10 to succeed in making famciclovir monohydrate. Applicants contend that, regardless the disclosures of Brand, it would not be undue experimentation for one skilled in the art to prepare famciclovir monohydrate according to the process of claim 35."But Brand teaches that the use of aqueous acetone gives famciclovir, not famciclovir hydrate, and applicants' argument simply ignores this fact. MPEP 2164.05 states, "Once the examiner has weighed all the evidence and established a reasonable basis to question the enablement provided for the claimed invention, the burden falls on applicant to present persuasive arguments, supported by suitable proofs where necessary" that the claims are indeed enabled. Brand provides the reasonable basis to doubt the statement in the specification, since Brandt does what the specification calls for and does not get the result that the specification sets forth.

Claims 74-77 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Pharmaceutically acceptable compositions cannot include unsafe organic solvents. Methanol is considered a toxin.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to /Mark L. Berch/ whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark L. Berch/
Primary Examiner
Art Unit 1624

3/20/2008